

IN THE CLAIMS (37 CFR 1.121 Revised)

1.- 2. (cancelled)

3. (currently amended) ~~The method of claim 1~~ A method of generating a pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds comprising the steps of

(i) generating a set of three-dimensional conformers for each of the compounds in a training set comprising five or more selective serotonin reuptake inhibitor compounds;

(ii) correlating each of the compounds of said training set with an observed value for CYP2D6 inhibitory potency;

(iii) generating from the conformers of step (i) a set of one or more pharmacophore test models, each said pharmacophore test model comprising three or more of the CYP2D6 enzyme active site features selected from the group consisting of the hydrogen bond donor feature, the hydrogen bond acceptor feature, the hydrophobic region feature, the ionizable region feature and the ring aromatic feature, arranged in three-dimensional space;

(iv) calculating the CYP2D6 inhibitory potency for each conformer generated in step (i) towards each of the pharmacophore test models generated in step (iii);

(v) calculating the total cost for each pharmacophore test model; and

(vi) choosing the lowest cost pharmacophore test model as the pharmacophore model;

wherein said steps are carried out with the molecular modeling software CATALYST™, version 4.

4.-15. (cancelled)

16. (withdrawn) A method of generating a pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds comprising the steps of

(i) correlating the chemical features of the conformers of the compounds in a training set of selective serotonin reuptake inhibitor compounds with a set of two- and/or three-dimensional descriptors for the active site of the CYP2D6 enzyme; and

(ii) generating an equation relating the observed CYP2D6 inhibitory potency of said selective serotonin reuptake inhibitor compounds to a set of generated two- and/or three dimensional descriptors for the selective serotonin reuptake inhibitor compound.

17. (withdrawn) The method of claim 16 wherein the steps are carried out using the set of two- and/or three-dimensional descriptors for selective serotonin reuptake inhibitor compounds

chosen from the 3D-QSAR functionality and the genetic function approximation equation of the CERIU²TM software program.

18. (withdrawn) The method of claim 16 wherein the CYP2D6 inhibitory potency is a value determined by *in vitro* of the inhibition of the CYP2D6 enzyme reaction with bufuralol, said value selected from the group consisting of the IC₅₀ value, the % inhibition value or the K_i (apparent) value.

19. (withdrawn) The method of claim 16 wherein the CYP2D6 is native or recombinant CYP2D6.

20. (withdrawn) A method for determining the CYP2D6 inhibitory potency of an selective serotonin reuptake inhibitor compound comprising the steps of

(i) generating the two- and/or three-dimensional descriptors for said selective serotonin reuptake inhibitor compound;

(ii) inputting said three-dimensional descriptors into an equation relating the observed CYP2D6 inhibitory activity of a set of selective serotonin reuptake inhibitor compounds to a set of three-dimensional descriptors generated for those selective serotonin reuptake inhibitor compounds; and

(iii) solving said equation for the CYP2D6 inhibitory activity of the selective serotonin reuptake inhibitor compound corresponding to the generated three-dimensional descriptors of step (i).

21. (withdrawn) The method of claim 20 wherein steps (i) through (iii) are carried out using a software program.

22. (withdrawn) The method of claim 21 wherein the software program is the CERIU²TM program

23. (cancelled)

24. (withdrawn) A pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds generated in accordance with the method of claim 16.

25. (withdrawn) A pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds according to claim 23 comprising 1 hydrogen bond acceptor, 1 hydrophobic feature and 1 hydrogen bond donor.

26. (currently amended) A pharmacophore model for the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitor compounds ~~according to claim 25~~ comprising 1 hydrogen bond acceptor, 1 hydrophobic feature and 1 hydrogen bond donor of the CYP2D6 enzyme active site features, arranged in three-dimensional space; wherein said features have the following centroids and vectors:

<u>Coordinates</u>	<u>Hydrogen Bond Acceptor</u>		<u>Hydrogen Bond Donor</u>		<u>Hydrophobic</u>
	<u>Vector</u>		<u>Vector</u>		
X	-2.73	-2.89	0.93	0.60	-1.66
Y	-1.83	-4.67	-1.69	-4.62	1.06
Z	0.12	-0.84	0.14	0.67	1.16

27. (withdrawn) A method for the identification of an selective serotonin reuptake inhibitor compound which does not possess significant inhibitory potency towards CYP2D6 comprising the steps of

- (i) generating two- and/or three-dimensional descriptors for an selective serotonin reuptake inhibitor compound;
- (ii) inputting said two- and/or three-dimensional descriptors for the selective serotonin reuptake inhibitor compound into the equation of claim 16;
- (iii) solving said equation for the inhibitory activity of the selective serotonin reuptake inhibitor compound corresponding to the generated two- and/or three-dimensional descriptors of step (i); and
- (iv) designating the compound as not being a significant inhibitor of CYP2D6 activity if the calculated $K_{i \text{ (apparent)}}$ value is greater than 1 μM .

28. (withdrawn) A method according to claim 27 where the calculated $K_{i \text{ (apparent)}}$ value is greater than 10 μM .

29. (withdrawn) A method according to claim 27 wherein the calculated $K_{i \text{ (apparent)}}$ value of step (iv) is greater than 100 μM .

30. (withdrawn) A selective serotonin reuptake inhibitor compound which does not possess significant inhibitory potency towards CYP2D6 identified by the method of claim 27.

31. (withdrawn) A pharmaceutical composition comprising an selective serotonin reuptake inhibitor compound, which does not possess significant inhibitory potency towards CYP2D6, according to claim 30.

32. (withdrawn) A method of treatment for a condition, disorder or disease for which an selective serotonin reuptake inhibitor compound is therapeutically useful comprising the administration of an selective serotonin reuptake inhibitor compound according to claim 30.

33. (withdrawn) A method according to claim 32 wherein the condition, disease or disorder is selected from the group consisting of nausea, asthma, migraine, arthritis, post-operative pain and depression.

34.-40. (cancelled)

41. (withdrawn) A computer-readable medium having stored thereon a pharmacophore model for selective serotonin reuptake inhibitor compounds which possess significant inhibitory potency towards CYP2D6 generated in accordance with the method of claim 16.

42. (withdrawn) A computer comprising a computer-readable medium according to claim 41.

43. (cancelled)